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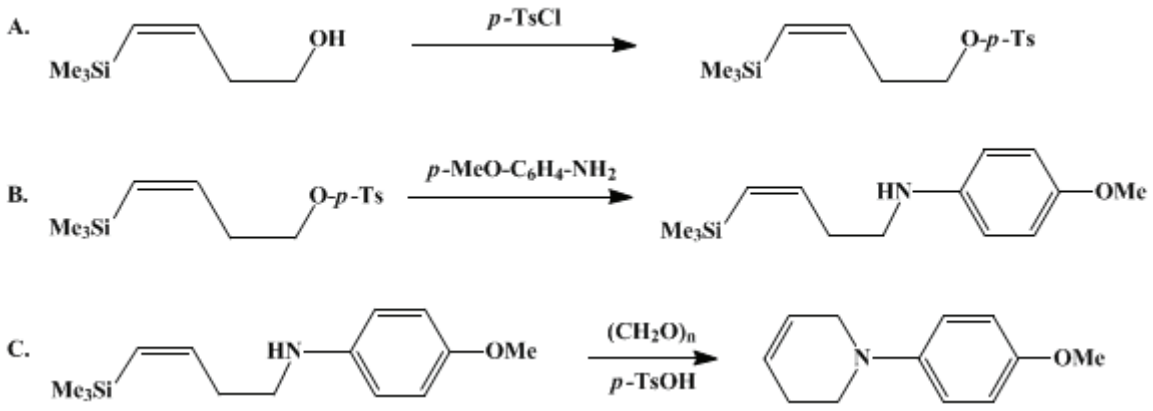
Organic Syntheses, Coll. Vol. 8, p.358 (1993); Vol. 68, p.188 (1990).

REGIOSELECTIVE SYNTHESIS OF TETRAHYDROPYRIDINES: 1-(4-METHOXYPHENYL)-1,2,5,6-TETRAHYDROPYRIDINE

[Pyridine, 1,2,3,6-tetrahydro-1-(4-methoxyphenyl)-]



Submitted by Larry E. Overman, Chris J. Flann, and Thomas C. Malone[1].
Checked by Ronald C. Newbold and Andrew S. Kende.

1. Procedure

A. *Preparation of (Z)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate*. An oven-dried, 1-L, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon or nitrogen. The flask is charged with 17.3 g (0.120 mol) of (Z)-4-(trimethylsilyl)-3-buten-1-ol (Note 1) and 290 mL of dry pyridine (Note 2). The reaction mixture is cooled to 0°C in an ice–water bath and 25.2 g (0.132 mol) of *p*-toluenesulfonyl chloride (Note 3) is added to the solution. When the *p*-toluenesulfonyl chloride is completely dissolved, the flask containing the reaction mixture is sealed and placed in a refrigerator at −20°C for 24 hr (Note 4). The reaction mixture is then poured into a rapidly stirring mixture of 200 g of ice and 200 mL of water contained in a 2-L Erlenmeyer flask. The resulting mixture is transferred to a 2-L separatory funnel and extracted with five 200-mL portions of ether. The combined organic phases are washed with five 200-mL portions of ice-cold aqueous 6 *N* hydrochloric acid (Note 5) and 200 mL of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 29.2 g (82%) of crude (*Z*)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate as a light-yellow oil (Note 6).

B. *Preparation of N-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine*. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a 250-mL addition funnel, and a gas inlet tube. The flask is flushed with argon or nitrogen and charged with 41.5 g (0.337 mol) of 4-methoxyaniline (Note 7) and then heated to 65°C. The stirring melt is degassed (Note 8), 20.2 g (67.8 mmol) of (*Z*)-4-(trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate is added over 15 min, and the resulting solution is maintained at 65°C for 3 hr. The reaction product is allowed to cool to ca. 50°C and is then transferred to a 500-mL separatory funnel using 250 mL of chloroform. The chloroform solution is washed with two 100-mL portions of 1 *M* sodium hydroxide and the combined aqueous phases are extracted with 500 mL of chloroform. The combined organic phases are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is distilled through a 17-cm Vigreux column and excess 4-methoxyaniline is collected in the first fraction, bp 80–86°C (0.25 mm) (Note 9). Vacuum distillation is continued to give 10.6 g (63% yield) of *N*-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, bp 125–128°C (0.25 mm), as a pale-yellow oil (Note 10).

C. *Preparation of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine*. An oven-dried, 250-mL, two-necked round-bottomed flask is equipped with a magnetic stirring bar, a reflux condenser, and an argon

or nitrogen inlet. The flask is flushed with argon or nitrogen, charged with 6.62 g (26.5 mmol) of *N*-(4-methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine, 7.45 g (260 mmol) of paraformaldehyde (Note 11), 4.8 g (25 mmol) of *p*-toluenesulfonic acid monohydrate (Note 12), and 100 mL of acetonitrile (Note 13). The reaction mixture is degassed (Note 8) and heated at reflux for 1 hr (Note 14). The reaction mixture is cooled to room temperature and the excess paraformaldehyde is removed by vacuum filtration. The reaction vessel is washed with two 25-mL portions of dichloromethane and the washings are clarified by filtration. The combined organic phases are concentrated under reduced pressure using a rotary evaporator, and the resulting solid residue is dissolved in dichloromethane and transferred to a 500-mL separatory funnel. The organic phase is washed with two 100-mL portions of 4 *M* sodium hydroxide and the aqueous washings are extracted with 50 mL of dichloromethane. The combined organic phases are then washed with 100 mL of water, dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude residue is dissolved in 9 : 1 hexane–ether and filtered through a 20-cm column (6-cm diameter) of silica gel. Evaporation of solvent gives 4.2 g (84% yield) of 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine as a white crystalline solid, mp 49–51°C (Note 15) and (Note 16).

2. Notes

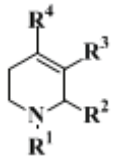
1. The trimethylsilyl butenol was prepared as described in another *Organic Syntheses* procedure (*Org. Synth., Coll. Vol. VIII*, **1993**, 609).
2. Pyridine is freshly distilled from calcium hydride under an argon atmosphere.
3. *p*-Toluenesulfonyl chloride was purchased from Aldrich Chemical Company, Inc. and was purified by dissolving 100 g in 100 mL of chloroform, adding 1250 mL of hexane, filtering to remove insoluble impurities, and concentrating the filtrate under reduced pressure.[2]
4. During this time, pyridinium hydrochloride precipitates from the solution as white needles.
5. Caution must be exercised so that the ether layer does not become too warm during this extraction.
6. The sample has the following spectral characteristics: IR (neat) cm^{-1}: 1610, 1365, 1255, 1180. ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.13 (s, 9 H, $SiCH_3$), 2.49–2.58 (m, 5 H), 4.14 (apparent t, 2 H, J = 6.9, CH_2OR), 5.69 (d, 1 H, J = 14.1, $R_3SiCH{=}CH$), 6.17 (overlapping dt, 1 H, J = 14.1 J = 7.2, $R_3SiCH{=}CH$), 7.40 (apparent d, 2 H, J = 7.8, aryl H), 7.85 (apparent d, 2 H, J = 8.3, aryl H). Gas-chromatographic analysis using a 25-m 5% methyl-phenylsilicone column showed that this sample was >92% pure and contained several unidentified impurities.
7. 4-Methoxyaniline (*p*-anisidine) was purchased from Aldrich Chemical Company, Inc.
8. This is done by applying a mild vacuum to the reaction vessel and then filling the vessel with argon or nitrogen. This operation was repeated 3 times.
9. The condenser is not cooled and the collector tip is at times gently heated with a heat gun to prevent crystallization of 4-methoxyaniline in the distillation apparatus.
10. The product had the following spectral characteristics: IR (neat) cm^{-1}: 3390, 2950, 1608, 1246, 1040, 838; ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.14 (s, 9 H, $SiCH_3$), 2.42–2.51 (apparent q, 2 H, J = 7, $=CHCH_2$), 3.15 (t, 2 H, J = 6.8, CH_2NR), 3.76 (s, 3 H, $ArOCH_3$), 5.67 (d, 1 H, J = 14.1, $R_3SiCH{=}CH$), 6.32 (overlapping dt, 1 H, J = 14.1 and 7.3, $R_3SiCH{=}CH$), 6.59 (apparent d, 2 H, J = 9.0, aryl H), 6.76 (apparent d, 2 H, J = 9.0, aryl H). High-resolution mass spectrum (EI, 70 eV) 249.1548 (calcd. for $C_{14}H_{23}NOSi$: 249.1549). Gas-chromatographic analysis using a 25-m 5% methylphenylsilicone capillary column showed that this sample was >95% pure. Two impurities of similar retention time, presumed to be the (*E*)-stereoisomer and the corresponding alkane, constitute 1–3% of the product mixture depending on the run, while a third, longer-retention-time impurity, the corresponding tertiary amine, represents 2% of the product mixture.
11. Paraformaldehyde was purchased from Alpha Products, Morton/Thiokol, Inc.
12. *p*-Toluenesulfonic acid monohydrate was purchased from Aldrich Chemical Company, Inc. and is suitable for use after storage for 24 hr in a vacuum desiccator over phosphorus pentoxide.
13. Acetonitrile was purchased from Mallinkrodt, Inc.
14. During this time paraformaldehyde can be seen forming on the inside of the reflux condenser.
15. The sample thus obtained is 94–97% pure by capillary GC analysis using a 25-m 5% methylphenylsilicone capillary column. This material gave the following elemental analysis. Anal. calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.49; H, 8.15; N, 7.31.
16. A purer sample may be obtained by vacuum sublimation at 60°C (0.3 mm). The material shows the following spectral characteristics: IR (KBr) cm^{-1}: 2831, 1514, 1249, 1210, 1190, 1035, 815; ^1H NMR

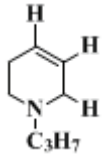
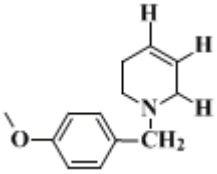
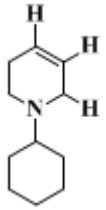
(250 MHz) δ: 2.4–2.7 (m, 2 H), 3.27 (t, 2 H, *J* = 5.6), 3.58–3.65 (m, 2 H), 3.80 (s, 3 H, OCH_3), 5.7–5.9 (m, 2 H, RCH=CHR), 6.85–6.95 (m, 4 H, aryl H). Gas-chromatographic analysis using a 25-m 5% methylphenylsilicone column showed that this material was 98% pure and was contaminated with 1.8% of the starting secondary amine and 0.3% of the corresponding tertiary acyclic amine. This material melts at 50–52°C and gave the following elemental analysis. Anal. calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.18, H, 8.00; N, 7.40. The oxalate salt melts at 134–135°C and gave the following elemental analysis. Anal. calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.09; N, 5.01. Found: C, 60.09; H, 6.16; N, 4.98.

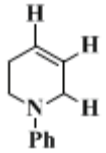
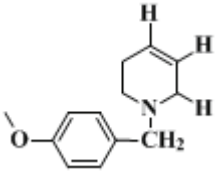
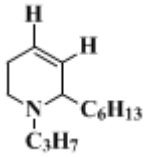
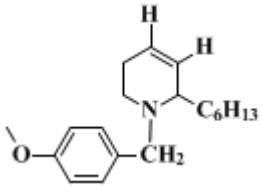
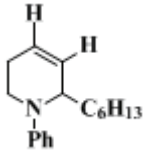
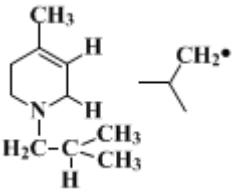
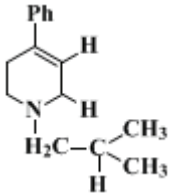
3. Discussion

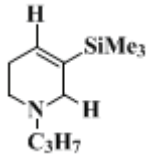
A variety of 1,2,5,6-tetrahydropyridines can be prepared by the reaction of (*Z*)-4-(trimethylsilyl)-3-butenamines with aldehydes.[3,4,5,6] Representative examples are summarized in Table I. Cyclizations with paraformaldehyde occur readily in refluxing acetonitrile, while cyclizations with other aldehydes require higher temperatures. Tetrahydropyridines with substituents at atoms −1, −2, −3, and −4 have been regioselectively prepared in this way. In no case was any trace of a regioisomeric tetrahydropyridine detected.

TABLE I
PREPARATION OF SUBSTITUTED 1,2,5,6-TETRAHYDROPYRIDINES[3,4]



R^1	R^2	R^3	R^4	Cyclization Step Conditions (Temp., °C; Time, hr)	Yield (%)
C_3H_7	H	H	H	80; 1.5	 61
4-Methoxybenzyl	H	H	H	80; 1.5	 91
Cyclohexyl	H	H	H	110; 10	 54[a]

Ph	H	H	H	80; 0.7	 61
4-Methoxyphenyl	H	H	H	80; 1	 84
C_3H_7	C_6H_{13}	H	H	120; 48	 54
4-Methoxybenzyl	C_6H_{13}	H	H	120; 72	 64
Ph	C_6H_{13}	H	H	80; 3	 68
Iso-C_4H_9	H	H	CH_3	80; 2	 66
Iso-C_4H_9	H	H	Ph	80; 2	 83

C_3H_7	H	$SiMe_3$	H	80; 1.2	
					82

[a]In this case the reaction of a cyanomethyl tertiary amine with silver trifluoroacetate in chloroform was used to initiate the cyclization instead of the reaction of an aldehyde with a secondary amine salt.

The 1,2,5,6-tetrahydropyridine ring is found in several natural products and numerous pharmacologically active materials.[5,6] This ring system is most commonly constructed by reduction of the corresponding pyridinium salt or from 4-piperidone precursors.[5] The cyclization approach reported here has the advantage of complete regiocontrol of the double-bond position. Moreover, this approach is of particular value for the synthesis of 1-aryl-substituted tetrahydropyridines that are difficult to access, since they are not generally available from pyridine precursors.

Iminium ion-vinylsilane cyclizations closely related to the one described here have been used to prepare indolizidine alkaloids of the pumiliotoxin A[7] and elaeokanine[3] families, indole alkaloids,[8] amaryllidaceae alkaloids,[9] and the antibiotic (+)-streptazolin.[10] The ability of the silicon substituent to control the position, and in some cases stereochemistry, of the unsaturation in the product heterocycle was a key feature of each of these syntheses.

Alternative methods of preparing 1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine have not been reported.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 609

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Indole (120-72-9)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

silver trifluoroacetate (2966-50-9)

p-Toluenesulfonyl chloride (98-59-9)

phosphorus pentoxide (1314-56-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

1-(4-Methoxyphenyl)-1,2,5,6-tetrahydropyridine,
Pyridine, 1,2,3,6-tetrahydro-1-(4-methoxyphenyl)- (133157-31-0)

(Z)-4-(Trimethylsilyl)-3-butenyl 4-methylbenzenesulfonate (87682-62-0)

(Z)-4-(Trimethylsilyl)-3-buten-1-ol (87682-77-7)

N-(4-Methoxyphenyl)-(Z)-4-(trimethylsilyl)-3-butenamine (133157-30-9)

4-methoxyaniline,
p-anisidine (104-94-9)

pyridinium hydrochloride (628-13-7)

4-piperidone

paraformaldehyde (30525-89-4)